

<b>Office Action Summary</b>	<b>Application No.</b> 10/592,962	<b>Applicant(s)</b> SIDRANSKY, DAVID
	<b>Examiner</b> JEANINE A. GOLDBERG	<b>Art Unit</b> 1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 20 January 2011.
- 2a) This action is FINAL.      2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1,2,5-7,10,11,13,15,16,18,37-39,44,45,51,52,54,58-63 and 69-73 is/are pending in the application.  
 4a) Of the above claim(s) 5,6,10,11,60,62,63,69 and 71-73 is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 1,2,7,13,15,16,18,37-39,44,45,51,52,54,58,59,61 and 70 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- 1) Notice of References Cited (PTO-892)  
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)  
 3) Information Disclosure Statement(s) (PTO/SB/08)  
 Paper No(s)/Mail Date 09/06, 12/06
- 4) Interview Summary (PTO-413)  
 Paper No(s)/Mail Date 2/11.
- 5) Notice of Informal Patent Application  
 6) Other: \_\_\_\_\_

**DETAILED ACTION**

1. This action is in response to the papers filed January 20, 2011. Currently, claims 1,2,5-7,10,11,13,15,16,18,37-39,44,45,51,52,54,58-63 and 69-73 are pending. Claims 5,6,10,11,60,62,63,69 and 71-73 have been withdrawn as drawn to non-elected subject matter.

***Election/Restrictions***

2. Applicant's election without traverse of Group I and Adenomatous polyposis coli (APC), Claims 1-2, 7, 13, 15, 16, 18, 37-39, 44-45, 51-52, 54, 58-59, 61, 70, in the paper filed January 20, 2011 is acknowledged.

The requirement is still deemed proper and is therefore made FINAL.

***Priority***

3. This application is a 371 of PCT/US05/08849, filed March 17, 2005 and claims priority 60/553,993, filed March 17, 2004.

The Bib data sheet seems to also include to 60/553,994, filed March 17, 2004, however the ADS sheet does not include the '994 application. Thus, no priority appears to be drawn to 60/553,994, filed March 17, 2004. The Bib data sheet will be fixed.

***Drawings***

4. The drawings are acceptable.

***Information Disclosure Statement***

5. The listing of references in the specification (pages 42-43) is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-2, 7, 13, 15-16, 18, 37-39, 44-45, 51, 54, 61, 70, are rejected under 35 U.S.C. 102(a) as being anticipated by Yegnasubramanian et al. (Cancer Research, Vol. 64, pages 1975-1986, March 2004).

Yegnasubramanian et al teaches hypermethylation of CpG Islands in primary and metastatic human prostate cancer. Yegnasubramanian teaches quantifying the promoter methylation from GSTP1 and APC in prostate cancers (abstract)(limitations of Claims 1, 2, 7, 18, 61, 70). Yegnasubramanian teaches that bisulfite modification of

DNA samples and quantitative real-time methylation specific PCR (RT-MSP) were used to ascertain the amount of converted input templates in each sample (page 1976, col. 2, Figure 1)(limitations of Claim 15, 16). Yegnasubramanian teaches benign prostates were obtained and analyzed (page 1976, col. 2). Yegnasubramanian also teaches WBC DNA was taken from the WBCs of healthy volunteers (Figure 1)(limitations of Claim 13). Table 2 provides primers for each gene analyzed including GSTP1 and APC. The promoter methylation was quantitated with real-time methylation specific PCR (RT-PCR)(page 1976, col. 2)(limitations of Claim 15-16). In particular Yegnasubramanian teaches GSTP1, APC, RASSF1alpha, PTGS2 and MDR1 were hypermethylated in >85% of prostate cancers but not in normal prostate cancers and tissues. Yegnasubramanian further teaches that using the markers in combination provided even more diagnostic power than using a single marker alone (page 1979, col. 2). Table 3 illustrates the sensitivity, specificity for each gene and several combinations of genes. All of these combinations include both GSTP1 and APC (page 1980). With respect to prognosis, Yegnasubramanian further states that the CpG islands that were frequently methylated in the primary cancers were also frequently methylated in the metastatic specimens (page 1984)(limitations of Claim 37-39, 44).

7. Claims 1-2, 13, 15-16, 18, 37-39, 44-45, 54, 70 are rejected under 35 U.S.C. 102(a) as being anticipated by Harden et al. (Clinical Cancer Research, Vol. 9, pages 1370-1375, April 2003).

Harden teaches gene promoter hypermethylation in tumors and lymph nodes of stage I lung cancer patients. In particular Harden teaches testing five gene promoters including GSTP1 and APC by real-time methylation-specific PCR in primary tumors from 90 stage I lung cancer patients for aberrant DNA methylation (abstract). Harden teaches using real-time QMSP (page 1370, col. 2)(limitations of Claim 15). To teach the relative levels of methylated promoter DNA in each sample, the values of the gene of interest were compared with the values of the internal reference gene to obtain a ratio that was then multiplied by 100 to give a percentage value (page 1371, col. 1)(limitations of Claim 16). Harden teaches that leukocyte DNA from a healthy individual was used as the negative control for all genes (page 1371, col. 2)(limitations of Claim 13). 8% of the primary tumors were methylated at GSTP1 and 72% at APC. Harden further analyzes the presence of tumor methylation as a marker to investigate the presence of occult metastasis in corresponding histologically negative lymph nodes (i.e. prognosis). Table 1 illustrates stage, histology, tumor methylation and lymph node methylation for the 90 stage I NSCLC cases. Harden teaches that APC and GSTP1 correlated with nonsquamous histology (page 1372, col. 1).

With respect to Claims 37 and 44, the recitation in the wherein clause sets forth an intended use for the claimed method and does not distinguish from the method of the prior art. There are no structural steps that differentiate the claimed method from that set forth in the art. The only method steps required by Claim 37 and 44 are quantifying the level of promoter methylation. Harden teaches this method step.

Harden teaches each method step required by the instant claims.

8. Claims 1-2, 7, 13, 15-16, 18, 37-39, 44-45, 51, 54, 61, 70 are rejected under 35 U.S.C. 102(b) as being anticipated by Maruyama et al. (Clinical Cancer Research, Vol. 8, pages 514-519, February 2002).

Maruyama teaches analyzing aberrant promoter methylation profiles of prostate cancers. In particular gene promoter methylation was analyzed in 101 prostate cancer samples (limitations of Claim 7). Among the genes analyzed were GSTP1 and APC (abstract)(limitations of Claim 18). Maruyama teaches analyzing prostate specimens using MSP assays (limitations of Claim 51). Maruyama teaches that negative control samples without DNA were included for each set of PCR. Moreover, the conditions for MSP were selected to distinguish between tumors and control tissues from healthy individuals (page 515, col. 2)(limitations of Claim 13, 15-16, 45). Maruyama teaches 101 prostate cancers and 32 nonmalignant prostate tissues were analyzed. The results demonstrate that GSTP1 and APC were methylated in prostate cancers at 36% and 27% respectively (page 515, col. 2). Table 3 illustrates that the frequency of aberrant methylation in prostate tissues differs significantly between cancers and nonmalignant tissues for both GSTP1 and APC. (page 516). Maruyama studies the tumor state and methylation patterns and both GSTP1 and APC were more frequently methylated in high state (Stage II or IV) as opposed to low stage (Stage I or II) (Figure 2, page 517)(limitations of Claim 37-39, 44). Maruyama specifically concludes that the methylation profile of prostate cancers correlates with clinicopathological features of poor prognosis (page 518, col. 2).

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claim 52 is rejected under 35 U.S.C. 103(a) as being unpatentable over Maruyama et al. (Clinical Cancer Research, Vol. 8, pages 514-519, February 2002) in view of Goessl et al. (Cancer Research, Vol. 60, pages 5941-5945, November 2000).

Maruyama teaches analyzing aberrant promoter methylation profiles of prostate cancers. In particular gene promoter methylation was analyzed in 101 prostate cancer samples (limitations of Claim 7). Among the genes analyzed were GSTP1 and APC (abstract)(limitations of Claim 18). Maruyama teaches analyzing prostate specimens

using MSP assays (limitations of Claim 51). Maruyama teaches that negative control samples without DNA were included for each set of PCR. Moreover, the conditions for MSP were selected to distinguish between tumors and control tissues from healthy individuals (page 515, col. 2)(limitations of Claim 13, 15-16, 45). Maruyama teaches 101 prostate cancers and 32 nonmalignant prostate tissues were analyzed. The results demonstrate that GSTP1 and APC were methylated in prostate cancers at 36% and 27% respectively (page 515, col. 2). Table 3 illustrates that the frequency of aberrant methylation in prostate tissues differs significantly between cancers and nonmalignant tissues for both GSTP1 and APC. (page 516). Maruyama studies the tumor state and methylation patters and both GSTP1 and APC were more frequently methylated in high state (Stage II or IV) as opposed to low stage (Stage I or II) (Figure 2, page 517)(limitations of Claim 37-39, 44). Maruyama specifically concludes that the methylation profile of prostate cancers correlates with clinicopathological features of poor prognosis (page 518, col. 2).

Maruyama does not specifically teach that patient samples for analyzing promoter methylation may be serum, plasma, ejaculate or urine.

However, at the time the invention was made, the prior art had analyzed methylation-specific PCR for DNA based detection of prostate cancer in bodily fluids. In particular Goessl teaches analysis of GSTP1, the most frequent DNA alteration in prostatic cancer with MSP in serum, plasma, ejaculate and urine. Maruyama teaches each of these samples demonstrated GSTP1 promoter methylation at detectable levels.

Therefore, at the time the invention was made, it would have been obvious to have modified the method of Maruyama which uses prostate tissues with a method relying on serum, plasma, ejaculate or urine. Goessl teaches that promoter methylation may be detected in serum, plasma, ejaculate and urine. The ordinary artisan would have been motivated to have used these samples instead of prostate tissue because they may be obtained by noninvasive detection means. The analysis of serum, plasma, ejaculate and urine do not require any surgery.

11. Claims 58-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maruyama et al. (Clinical Cancer Research, Vol. 8, pages 514-519, February 2002).

Maruyama teaches analyzing aberrant promoter methylation profiles of prostate cancers. In particular gene promoter methylation was analyzed in 101 prostate cancer samples (limitations of Claim 7). Among the genes analyzed were GSTP1 and APC (abstract)(limitations of Claim 18). Maruyama teaches analyzing prostate specimens using MSP assays (limitations of Claim 51). Maruyama teaches that negative control samples without DNA were included for each set of PCR. Moreover, the conditions for MSP were selected to distinguish between tumors and control tissues from healthy individuals (page 515, col. 2)(limitations of Claim 13, 15-16, 45). Maruyama teaches 101 prostate cancers and 32 nonmalignant prostate tissues were analyzed. The results demonstrate that GSTP1 and APC were methylated in prostate cancers at 36% and 27% respectively (page 515, col. 2). Table 3 illustrates that the frequency of aberrant methylation in prostate tissues differs significantly between cancers and nonmalignant tissues for both GSTP1 and APC. (page 516). Maruyama studies the tumor state and

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methylation patterns and both GSTP1 and APC were more frequently methylated in high state (Stage II or IV) as opposed to low stage (Stage I or II) (Figure 2, page 517)(limitations of Claim 37-39, 44). Maruyama specifically concludes that the methylation profile of prostate cancers correlates with clinicopathological features of poor prognosis (page 518, col. 2).

Maruyama does not specifically teach selecting a treatment following quantification of promoter methylation. Maruyama does teach that methylation of GSTP1 and APC are indicative of high stage prostate cancer. The ordinary artisan would have been motivated to have selected a treatment that is appropriate for the high stage predicted. Treatments for high stage prostate cancer are known in the art including chemotherapy and surgery. Thus, it would have been obvious at the time the invention was made to have identified patients with methylation at GSTP1 and APC and selected a treatment for these patients.

### ***Conclusion***

#### **12. No claims allowable over the art.**

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Nguyen, can be reached on (571)272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status

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information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

*/Jeanine Goldberg/*

**Primary Examiner**

March 11, 2011